Remarks

Support for the Amendments

Support for the foregoing amendments to claims 35, 60-65, 78, 99-101, 115, 135-137, 159, 170-175, 187 and 198-200 can be found throughout the specification. Specifically, support for the foregoing amendments can be found at page 22, line 15, through page 26, line 15. Hence, these amendments do not add new matter and their entry and consideration are respectfully requested.

Status of the Claims

By the foregoing amendments, claims 35, 60-65, 78, 99-101, 115, 135-137, 159, 170-175, 187 and 198-200 are sought to be amended. Upon entry of the foregoing amendments, claims 35-227 are pending in the application, with claims 35, 78, 115, 151, 159, 187 and 213 being the independent claims. Claims 151-157 and 213-225 have been allowed.

Summary of the Office Action

In the Office Action dated September 22, 2004, the Examiner has made four rejections of the claims. Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

The Rejections Under 35 U.S.C. § 112, First paragraph

In the Office Action at page 2, the Examiner has rejected claims 57-58, 96-97, 132-133 and 196-197 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

The Examiner contends that there is no literal support for the phrase "immediately adjacent to" recited in the present claims. Applicants respectfully disagree with this contention. Applicants submit that the term "immediately adjacent" would be readily understood by the ordinarily skilled artisan to mean that the recombination sites and the related genes, portions of genes, etc., have no intervening nucleotides between them. To demonstrate exemplary support for this phrase, the Examiner's attention is directed to Example 6, at pages 47-51 of the present specification, as well as Figures 8B, 8I and 8J. Each of the vectors depicted in Figures 8B, 8I and 8J, contains a recombination site (e.g., *att*R1) located "immediately adjacent" to a GST gene.

The ordinarily skilled artisan would readily understand that the orientation depicted in these Figures represents a recombination sites "immediately adjacent" to a related gene. Applicants therefore respectfully submit that there is sufficient literal support for the phrase "immediately adjacent" in the present application. Hence, contrary to the Examiner's contentions, this term is not impermissible new matter. Applicants therefore respectfully request reconsideration and withdrawal of this rejection.

In the Office Action at page 3, the Examiner has next rejected claims 35-150, 159-212 and 226-227 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants therefore respectfully traverse this rejection.

The Examiner contends that there is no literal support for the phrase "wherein said at least one recombination protein is not a transposase." Applicants respectfully disagree with this contention. Applicants submit that the present specification provides sufficient literal support for this phrase such that the ordinarily skilled artisan would readily understand that

Applicants had possession of the claimed subject matter as of the filing date of the present application.

In one embodiment, the present invention is directed to the use of site-specific recombinases in site-specific recombination reactions. The present specification distinguishes site-specific recombination from "homologous recombination and transposition by a high degree of specificity for both partners." *See* specification at page 17, lines 6-8. The present specification further provides an overview of transposases at page 3, line 25 through page 4, line 8, distinguishing them again from site-specific recombinases that are useful in the practice of the present invention. Hence, Applicants respectfully submit that the present specification provides sufficient literal support for the phrase "wherein said at least one recombination protein is not a transposase."

However, solely to expedite prosecution, and not in acquiescence to this rejection, the phrase "wherein said at least one recombination protein is not a transposase" has been removed from the currently pending claims. Applicants reserve the right to prosecute claims directed to this embodiment in other divisional or continuation applications. Hence, in view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of this rejection.

The Rejection Under 35 U.S.C. § 102(b) Over Johnson

In the Office Action at pages 3-6, the Examiner has maintained the rejection of claims 35-71, 74-77, 158-180 and 183-186 under 35 U.S.C. § 102(b), as being anticipated by Johnson *et al.* WO 93/19172 (hereinafter "Johnson"). Applicants respectfully traverse this rejection.

Present claim 35 (and hence claims 36-71, 74-77 and 158 that depend ultimately therefrom and that are also rejected over Johnson) recites a method of producing a nucleic acid molecule comprising: providing a first nucleic acid molecule comprising at least a first gene or portion thereof and at least a first recombination site; providing a second nucleic acid molecule comprising at least a second gene or portion thereof and at least a second recombination site; and forming a mixture *in vitro* between the first and second nucleic acid molecules and at least one site-specific recombination protein, under conditions sufficient to cause recombination *in vitro* between the first and second recombination sites, thereby producing a third nucleic acid molecule in which the first and second genes or portions thereof are operably linked to form a functional gene.

Present claim 159 (and hence claims 160-180 and 183-186 that depend ultimately therefrom and that are also rejected over Johnson) recites a method of producing a nucleic acid molecule comprising: providing a first nucleic acid molecule comprising at least one promoter located immediately adjacent to at least a first recombination site; providing a second nucleic acid molecule comprising at least one gene or portion thereof located immediately adjacent to at least a second recombination site; and forming a mixture *in vitro* between the first and second nucleic acid molecules and at least one site-specific recombination protein, under conditions sufficient to cause recombination *in vitro* between the first and second recombination sites, thereby producing a third nucleic acid molecule in which the at least one promoter and the at least one gene or portion thereof are operably linked to form a functional gene.

Present independent claims 35 and 159 are drawn to methods in which the recombination reaction takes place *in vitro*.

As discussed in Applicants' previous reply of June 23, 2004, which is incorporated by reference herein in its entirety, Johnson does not enable *in vitro* recombination and therefore is not a proper § 102 reference. The ordinarily skilled artisan would have had to undertake extensive, undue experimentation to practice the methods of Johnson *in vitro*. As set forth in *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), such undue experimentation precludes enablement under 35 U.S.C. § 112, first paragraph. Johnson provides no experimental details in support of *in vitro* recombination, as all of the Examples in Johnson are limited to *in vivo* recombination (*see, e.g.,* Johnson in Example 1, at page 45, and in Example 2, at page 51). Johnson supplies no guidance or working examples of *in vitro* recombination that would allow the ordinarily skilled artisan to practice the presently claimed *in vitro* recombination methods without undue experimentation.

As discussed in Applicants' previous reply, the difficulties with performing *in vitro* recombination were specifically overcome by the present invention, not the cited art. The Examiner's attention is directed to the Examples at pages 31-51 of the present specification, where the various reaction conditions and buffers necessary for carrying out the *in vitro* recombination methods of the present invention are provided. Applicants respectfully submit that the experimentation required to develop these methods, reaction conditions and buffers, was far from routine as the Examiner has suggested, and these *in vitro* methods were made possible only by the disclosure of the present invention.

The Examiner points to Boyd in an attempt to cure Johnson's lack of enablement of *in vitro* recombination:

> While it may have been true at the time of the Johnson *et al.* application that it would have required some experimentation to optimize recombination reaction conditions, such experimentation would have been routine, as

> indicated by both the Johnson *et al.* and Boyd *et al.* references (e.g. Boyd *et al.* teach that Cre-mediated recombination *in vitro* is efficient and Johnson teach a methodology that can be readily used to determine whether the desired recombination products are formed).

Office Action at pages 5 and 6. Applicants respectfully disagree.

The experiments required to enable the *in vitro inter*molecular recombination methods of the present invention are far from routine. Boyd certainly does not provide disclosure of *in vitro* intermolecular recombination. The disclosure of Boyd is instead limited to *intra*molecular recombination; specifically, recombination between two *lox* sites on the *same* nucleic acid molecule (*see* Boyd at page 817, abstract, lines 8-12, "circular recombinant molecules are efficiently excised from the ligation products by Cre recombinase acting on pairs of *lox* sites within directly repeated vector molecules flanking insert DNA."). The ordinarily skilled artisan, even guided by the disclosure of Boyd, would not have been able to practice the *inter*molecular recombination methods of Johnson, *in vitro*, without significant undue experimentation, as Boyd does not teach how to perform *in vitro inter*molecular recombination. The difficulties with performing *in vitro* intermolecular recombination were specifically overcome by the present invention, not the related art as suggested by the Examiner. As stated in the present specification, "[i]t is unexpectedly discovered in the present invention that subcloning reactions can be provided using recombinational cloning." Specification at page 12, lines 4-5.

The Examiner is reminded that, under 35 U.S.C. § 102, a claim can only be anticipated by a publication if the publication describes the claimed invention with sufficient enabling detail to place the public in possession of the invention. *See In re Dono*hue, 766 F.2d 531, 533 (Fed. Cir. 1985); *see also PPG Industries, Inc. v. Guardian Industries Corp.*,

75 F.3d 1558, 1566 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter."). For at least the reasons discussed above, Applicants respectfully submit that Johnson does not describe the presently claimed invention. Hence, Johnson cannot and does not anticipate claims 35-71, 74-77, 158-180 and 183-186.

Applicants respectfully submit that, 1) Johnson does not enable the *in vitro* methods of the present invention; 2) the level of ordinarily skill in the art does not support the contention that the experimentation required to practice the methods of Johnson *in vitro* would have been routine; and 3) Boyd does not provide disclosure of *in vitro* recombination between a first and a second acid molecule, and hence, the disclosure of Boyd does not support the contention that the methods of Johnson could have been practiced *in vitro* without performing undue experimentation.

In view of the foregoing remarks, Applicants respectfully assert that Johnson is a deficient reference, and cannot be relied upon to reject the presently claimed invention under 35 U.S.C. § 102(b). Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 35-71, 74-77, 158-180 and 183-186 under 35 U.S.C. § 102(b) over Johnson.

The Rejection Under 35 U.S.C. § 112, Second Paragraph

In the Office Action at pages 6-7, the Examiner has rejected claims 57-58, 96-97, 132-133 and 196-197 under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection.

The Examiner contends that the phrase "immediately adjacent" is not defined in the present specification and it is unclear what the structural/functional requirements are for satisfying this limitation. Applicants respectfully disagree with this contention.

As discussed above, Applicants respectfully submit that the ordinarily skilled artisan would readily understand that the term "immediately adjacent" means that the recombination sites and the related genes, portions of gene, etc., have no intervening nucleotides between them. Applicants respectfully submit that the ordinarily skilled artisan reading the present specification, and specifically Figures 8B, 8I and 8J, would understand the meaning of this phrase. Hence, Applicants respectfully submit that the phrase "immediately adjacent" is not indefinite.

In view of the foregoing remarks, Applicants respectfully request that the rejection of claims 57-58, 96-97, 132-133 and 196-197 under 35 U.S.C. § 112, second paragraph, be reconsidered and withdrawn.

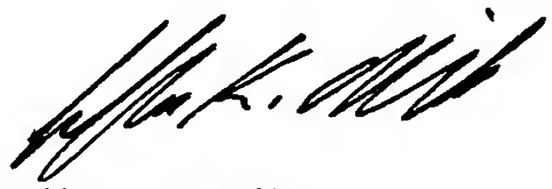
Conclusion

All of the stated grounds of rejection have been properly traversed or otherwise overcome. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn.

Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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